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Original Research

Diagnostic value of the APRI score in pregnant women infected with COVID-19

Diagnosis of COVID-19 in pregnancy

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Abstract
Aim: There are several methods to diagnose COVID-19. Early diagnosis and treatment are important in pregnant women with COVID-19. This study aims to investigate whether the APRI score is a method that can be used in the diagnosis of COVID-19 in pregnancy.
Material and Methods: A cross-sectional retrospective study was conducted between March 2020 and November 2020. Pregnant women who were found to be COVID-19 positive by the RT-PCR test were included in the study. The same number of healthy pregnant women who were matched for age, BMI, and gestational week without any systemic disease were included as a control group. Age, gravida, parity, gestational week, BMI, mode of delivery, complete blood count, liver function tests, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and APRI scores were evaluated. The sensitivity and specificity of NLR, PLR, and APRI score in the diagnosis of COVID-19 were investigated.
Results: Gravida, parity, gestational week, body mass index, and rate of previous vaginal delivery were similar between PCR-positive and negative patients. PCR-positive patients had significantly higher APRI scores (0.4±0.3 vs 0.2±0.0), NLR scores (7.7±5.3 vs 4.2±1.9) and PLR scores (217.3±105.7 vs 140.8±57.6) than PCR negative patients. The sensitivity of the NLR to detect COVID-19 was 69.44%, the specificity was 77.5%, the sensitivity of the PLR to detect COVID-19 was 58.33% (CI = 40.8–74.5), and the specificity was 87.5%. The APRI score sensitivity was 80.56%, and specificity was 80.0%.
Discussion: The APRI score can be useful in predicting COVID-19 infection in pregnant women.

Keywords
COVID-19 Disease, Pregnancy, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, APRI Score

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Introduction

Coronaviruses (CoV) are a large family of viruses that can cause mild infections such as the common cold or more severe illnesses such as Severe Acute Respiratory Syndrome (SARS) [1]. "COVID-19" (2019-nCoV Disease) started in Wuhan, China, for the first time in December, spread worldwide, and began to be seen in our country since March 2020 [Available at: https://covid19bilgi.saglik.gov.tr/tr/.]. The clinical picture due to COVID-19 virus could be asymptomatic, carriage may be in the form of mild upper respiratory tract infection or severe pneumonia resulting in mortality [Available at: https://www.cdc.gov/coronavirus/2019-ncov/index.html]. According to the WHO's COVID-19 report, the fatality rate of the People's Republic of China was reported as 3.8% and 2.6% in our country [Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019].

Pregnancy is a condition that predisposes women to viral infections and respiratory complications. Studies conducted at the beginning of the pandemic did not report increased susceptibility to COVID-19 infection in pregnant women than in the general population [2,3]. However, the meta-analysis showed that pregnancy is an increased risk factor for severe disease [4,5].

The diagnosis of COVID-19 infection is made by detecting specific sequences of virus RNA with a NAAT (nucleic acid amplification test) such as real-time reverse transcription-polymerase chain reaction (rRT-PCR) [Available at: https://www.quidel.com/immunoassays/rapid-sars-tests/sofia-sars-antigen-fia,]. Besides, other methods such as serological tests (antigen, antibody detection), computerized tomography are also used for diagnosis [6]. However, PCR testing is an expensive method, requiring equipment and time-consuming results [6].

Aspartate aminotransferase to Platelet Ratio Index (APRI) is a calculation method that is frequently used in clinical practice, can be calculated easily, and can detect inflammation and significant fibrosis in liver diseases at a considerable rate [7].

The study aims to investigate whether there is a difference between pregnant women diagnosed with COVID-19 and healthy pregnant women in terms of whole blood parameters and APRI score and to investigate whether the APRI score is a method that can be used in the diagnosis of COVID-19 in pregnancy.

Material and Methods

This cross-sectional retrospective study included pregnant women admitted to our hospital between March 2020 and November 2020 and were found to be COVID- 19 positive by RT-PCR test. The same number of healthy pregnant women who were matched for age, Body mass index (BMI), and gestational age without any systemic disease were included in the study as a control group.

Ethical Approval: The study was approved by the Institutional Review Board (IRB) of Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Ankara, Turkey (02.2021/02-04).

COVID-19 diagnosis

Nasopharyngeal swab samples of patients who applied to the COVID service of our hospital were detected in the Microbiology Reference Laboratory by the General Directorate of Public Health of the Ministry of Health, according to the epidemiology and diagnostic guide of COVID-19 infection, and a diagnosis was made by detecting rRT-PCR positivity [Available at:https://covid19.saglik.gov.tr/Eklenti/39551/0/covid19rehberigenelbilgilerepidemiyolojivetanipdf.pdf]. All diagnosed patients were referred to the pandemic hospital for follow-up and treatment after their condition had stabilized.

NLR was calculated as the ratios of the absolute neutrophil count to the absolute lymphocyte count. PLR was calculated as the ratios of the absolute platelet count to the absolute lymphocyte count. The APRI score was defined as the AST/upper limit of normal range/platelet count (109/L)×100. The upper limit of normal for AST was accepted as 40 U/L.

Age, gravida, parity, gestational week, BMI, previous delivery type, symptoms, complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, D-dimer, activated partial thromboplastin time (aPTT), prothrombin time (PT), Sodium (Na), Potassium (K), Chloride (Cl), total bilirubin, lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), c-reactive protein (CRP), troponin, ferritin, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and APRI score were evaluated retrospectively from PCR-positive patients records. Age, gravida, parity, gestational week, BMI, previous delivery type, complete blood count, AST, ALT, NLR, PLR, and APRI score of the control group were also recorded.

It was aimed to determine whether there was any difference in APRI score, NLR, PLR between pregnant women with COVID-19 positive and the control group, and the sensitivity and specificity of APRI score in detecting COVID-19.

Statistical analyses

Statistical evaluation was performed using the Statistical Package for Social Sciences version 23 software (SPSS Inc., Chicago, IL, USA) and MedCalc. The visual (Q-Q plots and histograms) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) were used to assess the normality of variables. Continuous variables were stated as mean ± standard deviation (SD), median (Md), and minimum-maximum values. Categorical variables were indicated as frequency (n) and percentage (%). The Mann-Whitney U test was used to compare continuous variables with non-normal distribution. The receiver operating characteristic curve (ROC curve) was drawn for the two groups with differences. Area under the curve (AUC) was calculated to estimate the predictive power of the APRI, NLR, and PLR score for predicting RNA RT-PCR results. The sensitivity, specificity, positive predictive values, and negative predictive values of the statistically significant cut-off values were calculated. Statistical significance level was accepted as $p<0.05$.

Results

Descriptive and Preliminary Statistics

The most common symptom in PCR positive patients cough (n = 19, 52.8%), and more than half of the patients had these complaints (n = 20, 55.5%). The cesarean section (CS) births in PCR positive patients (Md = 1.0) were significantly higher than in PCR-negative patients (Md = 0.0) (p=0.001). However, no significant differences were found between PCR negative and positive patients in gravida, parity, gestational week, body

mass index, and rate of vaginal delivery (p > 0.05 for all) (Table 1).

The AST value was significantly higher in PCR-positive patients (24.3±7.2) than in PCR-negative patients (18.0±3.4) (p < 0.001). However, the creatinine value was significantly higher in PCR-

Table 1. Baseline characteristics of the patients

	RNA RT-PCR1 Positive (n = 36)	RNA RT-PCR1 Negative (n = 40)	p
Gravida *	2.0 (1-7)	3.0 (1-6)	0.285
Parity *	1.0 (0-4)	1.0 (0-3)	0.314
Gestational weekσ	28.2±3.0	27.0±1.9	0.591
BMIσ	24.8±2.9	23.7±2.1	0.127
Previous delivery type *			
Vaginal	1.0 (0-4)	1.0 (0-2)	0.716
C/S	1.0 (0-2)	0.0 (0-2)	0.001
Days of the symptomsσ	2.8±1.1	-	-
Most common symptoms n (%)		-	-
Cough	20 (55.5)		
Fatigue + asthenia	15 (41.7)		
Fever	9 (25)		
Admitting diagnosis n (%)		-	-
Cough	19 (52.8)		
Flu	5 (13.9)		
Diarrhea	4 (11.1)		
Preterm labor	2 (5.6)		
Fatigue + Muscle or body aches	2 (5.6)		
PPROM	1 (2.8)		
Shortness of breath	1 (2.8)		
Fever	1 (2.8)		
Fever + Cough	1 (2.8)*		

BMI: Body mass index, CS: cesarean section PPROM: Preterm premature rupture of membranes * Data presented as median (min-max). σ Data presented as mean±SD.

Table 2. Comparison of laboratory results for PCR negative and positive patients

Laboratory Parameters	RNA RT-PCR1 Positive (Mean ± SD)	RNA RT-PCR1 Negative (Mean ± SD)	p
AST (U/L),	24.3±7.2	18.0±3.4	<0.001
ALT (U/L),	15.8±9.0	14.8±5.4	0.905
BUN (mmol/L)	6.9±2.5	7.5±2.3	0.189
Creatinine (µmol/L)	0.5±0.1	0.6±0.5	0.002
D-dimer (mg/L)	1.4±0.7	-	-
Troponin (ng/mL)	0.1±0.0	-	-
Fibrinogen (mg/dL)	442.7±90.8	-	-
CRP (mg/L),	26.5±30.8	-	-
Ferritin(ng/mL)	35.1±36.7	-	-
Total bilirubin (mg/dL)	0.5±0.3	-	-
LDH (U/L)	219.1±64.2	-	-
CK-MB(IU/L)	16.8±9.0	-	-
aPTT(sec)	29.3±4.1	-	-
PT(sec)	8.4±0.6	-	-
Na (mEq/L)	135.1±2.4	-	-
K(mmol/L)	4.5±4.5	-	-
Cl (mEq/L)	103.7±2.3	-	-

AST: aspartate aminotransferase ALT: alanine aminotransferase BUN: Urea CRP: C-reactive protein LDH: lactate dehydrogenase CK-MB: creatine kinase -MB aPTT: Activated partial thromboplastin time PT: Prothrombin time

Table 3. Comparison of APRI, NLR, and PLR score for PCR negative and positive patients

Variables	RNA RT-PCR1 Positive Mean ± SD	RNA RT-PCR1 Negative Mean ± SD	p
APRI	0.4±0.3	0.2±0.0	<0.001
NLR	7.7±5.3	4.2±1.9	0.001
PLR	217.3±105.7	140.8±57.6	<0.001

APRI: AST-to- Platelet Ratio Index, NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio

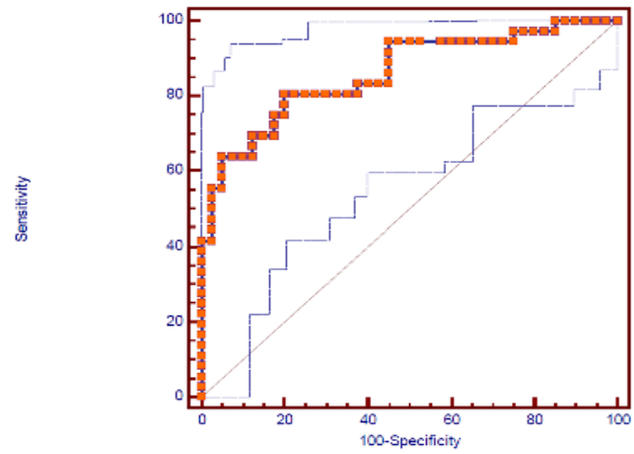

Figure 1. Receiver–operator curves analysis for APRI score

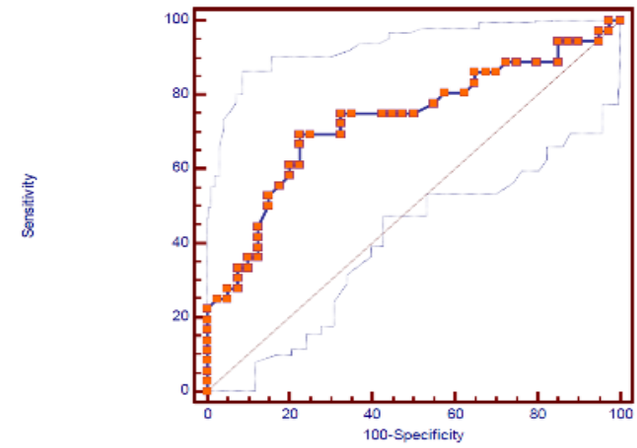

Figure 2. Receiver–operator curves analysis for NLR score.

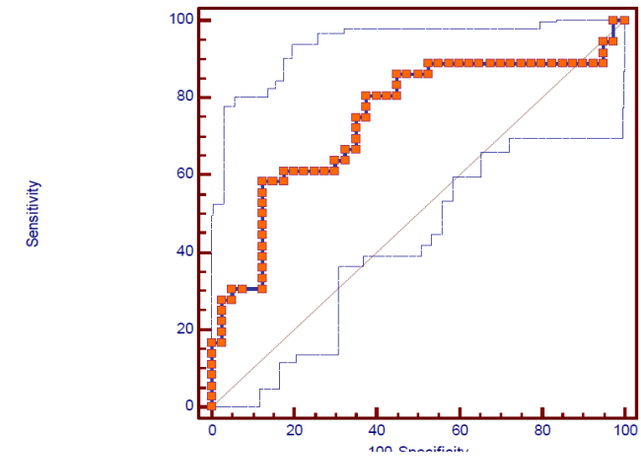

Figure 3. Receiver–operator curves analysis for PLR score.

negative patients (0.6 ± 0.5) than in PCR-positive patients (0.5 ± 0.1) (p=0.002). There were no significant differences between PCR-negative and positive patients in ALT and BUN levels (p > 0.05 for both) (Table 2).

PCR-positive patients had significantly higher APRI scores (0.4±0.3) than the PCR-negative patients (0.2±0.0) (p < 0.001). Similarly, PCR-positive patients had significantly higher NLR scores (7.7±5.3) than PCR-negative patients (4.2±1.9) (p = 0.001). Lastly, PCR-positive patients have significantly higher PLR score (217.3±105.7) than PCR-negative patients (140.8±57.6) (p < 0.001) (Table 3).

ROC analysis for NLR, PLR, and APRI Indexes

APRI Score

According to ROC analysis, AUC values of APRI score were .860 (SE = 0.043) (CI = 0.761– 0.929) p < 0.001, and were considered acceptable in the diagnosis of SARS-CoV-2. Diagnostic sensitivity was 80.56 (CI = 64.0–91.8) and the 1-specificity was 0.200 (i.e., the true negative rate indexing the specificity of the model was 80.0 CI = 64.4–90.9). The optimal cut-off value for APRI is >0.202 based on these criteria (Figure 1).

NLR Score

To find the cutoff point of NLR, the ROC analysis was conducted and AUC value was 0.731 (SE = 0.060) (CI = 0.616– 0.826) p < 0.001. The true positive rate indexing the sensitivity of the model was 69.44 (CI = 51.9–83.7), and the false positive rate (1-specificity) was 0.225 (i.e., the true negative rate indexing the specificity of the model was 77.5. (CI = 61.5–89.2). ROC curve analysis suggested the optimum NLR cutoff value >4.8 as seen in Figure 2.

PLR Score

ROC analysis revealed that the AUC values of PLR were statistically significant, AUC = 0.742 (SE = 0.060) (CI = 0.629–0.836) p < 0.001. With a PLR optimal cut-off value of >181.33, the true positive rate indexing the sensitivity of the model was 58.33 (CI = 40.8–74.5), and the false positive rate (1-specificity) was 0.125 (i.e., the true negative rate indexing the specificity of the model was 87.5 (CI = 73.2–95.8) (Figure 3).

Discussion

In this study, sensitivity and specificity of NLR, PLR, and APRI score in the diagnosis of COVID-19 were investigated in pregnant women. The sensitivity of the NLR to detect COVID-19 was 69.44%, the specificity was 77.5%, the sensitivity of the PLR to detect COVID-19 was 58.33% (CI = 40.8–74.5), and the specificity was 87.5%. APRI score sensitivity was 80.56%, and specificity was 80.0%.

Information about the 2019-nCoV disease is gradually increasing, and more information can be obtained with the publication of reviews and meta-analyzes in recent months. In the literature, symptoms of COVID-19 in pregnant women were similar to the non-pregnant patients and the general population, however, pregnancy is a risk factor for severe disease [8]. In the review by Islam et al., including 235 COVID-positive pregnant women, fever (58.72%), cough (47.23%), and sore throat (8.93%) were the most common symptoms, besides, neutrophil count, serum levels of CRP, ALT, and AST were high, and lymphocyte count and albumin levels were low [9]. In the meta-analysis published by Khalil et al., the most common symptoms in pregnant women positive for COVID-19 are fever (63.3%), cough (71.4%), and dyspnea (34.4%). The most common laboratory findings are increased CRP, transaminases, and lymphopenia [10]. The most common symptoms were cough, weakness, and fever in our study, following the literature. According to the normal reference values, serum CRP and D-dimer levels were found to be elevated in COVID- positive pregnants.

The diagnosis and general management of COVID-19 in pregnant women are similar to that in the general population. Several methods are recommended to diagnose the disease, such as RT-PCR test, computed tomography, antigen testing, and viral culture, etc. [11]. Despite there is still no gold standard test for diagnosis, the most commonly preferred test around the world and also recommended by WHO, is the RT-PCR test [Available at: https://www.who.int/publications/i/item/diagnostic-testing-for-sars-cov-2]. The sensitivity of the RT-PCR was reported as 85.7% for inpatients, 95.5% outpatients, and 89.9% for all patients by Kortela et al [12]. In a systematic review and meta-analysis, for RT-PCR test, nasopharyngeal swab sensitivity was 85%, the nasal swap was 86%, throat swabs 68%, the specificity ranged from 97% to 99% [13]. Compared to CT scan and RT -PCR testing, the sensitivity of CT scan was 95%, which is higher than RT-PCR (91%). The specificity of CT and RT-PCR was 31% and 100% [14]. Despite its high sensitivity and specificity, RT-PCR test has disadvantages in terms of expensiveness, time-consuming results, and required experts.

NLR, PLR, and APRI score indices are parameters obtained from hemogram parameters and correlated with inflammation. The frequency of usage of these parameters has been increasing in the obstetrics practice in recent days [15,16]. Ming-Zhu Yin et al. evaluated 31 pregnant and 30 non-pregnant women infected with COVID-19 in comparison of NLR, PLR and APRI scores, they found NLR, PLR and APRI scores were higher in pregnant women than in non-pregnant women [17]. Additionally, they found that NLR and Systematic immune-inflammation-based prognostic index (SII) were higher in patients with severe pneumonia. Our study revealed that APRI score with a sensitivity of 80.56 % and specificity of 80.0% could be a diagnostic marker of the COVID-19 infection in pregnancy.

Pregnancy can compromise the immune system, and potentially, COVID-19 infection can increase the risk of pulmonary infection in pregnant patients compared to non-pregnant patients. Evaluation of the elevated risk for COVID-19 infection is very important for taking precautions in pregnancy [18]. Increased inflammatory index scores in the routine hemogram parameters could give clinicians tricks for making early diagnosis and appropriate management.

Some limitations should be considered in results of this study. First, there are data with a small number of patients. Secondly, since we do not have intensive care conditions, the patients' follow-up and treatment are not performed in our hospital, so maternal and neonatal outcomes could not be evaluated. Third, we only include hospitalized pregnant patients with laboratory confirmed COVID-19.

Conclusion

Inflammatory index scores, including NLR PLR and APRI score, are non-invasive diagnosis tools. To make a diagnosis, the availability of a rapid, cost-effective, simple, and easy test is

essential. These inflammatory index scores, especially the APRI score, can be useful in recognizing and predicting COVID-19 infection in pregnant women.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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